REMARKS

Applicants respectfully request reconsideration of the instant application pursuant to 37 C.F.R. §1.112, and in light of the remarks which follow.

Objection to the Specification

Applicants traverse the objection to the specification. The layout and content of the application set forth in the Official Action are merely guidelines. MPEP § 601.I. Those guidelines illustrate the preferred layout and content of the application, and are merely suggestions for applicants' use. MPEP § 601.I. The specification satisfies the requirements for making an application for patent. 35 USC § 111. Applicants request reconsideration and withdrawal of the objection, and further examination of the application in its present form.

Rejection Under §112, 1st Paragraph

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph. It is asserted that the claim lacks support in the written description of the specification. Applicants traverse the rejection.

The rejection acknowledges that the specification includes a written description of the USP definition of neutral microgranules, i.e., granules comprising between 62.5 and 91.5 % sucrose. The rejection asserts, however, that this is the "background of the invention" section of the specification. The rejection cites no support for the implicit assertion that the location of the definition should deny its inclusion as within the written description.

The background provides the context in which the present invention is described and distinguished from the prior art. It is where applicants have described accepted principles and terms that relate to the instant invention. It is also where applicants have described how various prior art attempts to achieve some of applicants' objectives have been constructed, and how they differ from the claimed invention. It is an entirely appropriate and logically consistent choice for introducing known and accepted terminology. That is precisely what applicants have done. The USP definition of "neutral microgranules" is expressly set forth within the specification and adopted by applicants. Moreover, the term is used consistently throughout the remainder of the specification.

The rejection alleges, however, that applicants became their own lexicographer and explicitly defined "neutral microgranules" as spherical granules comprising "less than 91.5% of sucrose." This mischaracterizes applicants' statement, and ignores applicants' consistent use of the term throughout the specification.

Nowhere do applicants urge any alternate definition of "neutral microgranules"; nor do applicants suggest that neutral microgranules should be construed as granules having any amount of sucrose less than 91.5%. Rather, applicants' written description makes it quite clear that they are merely reciting one of many characteristics of embodiments of the invention that are merely exemplary and particularly preferred. Specification, page 10, lines 35-37 ("Neutral microgranules *particularly valued* in the context of the invention comprise less than 91.5% of sucrose."). Taken in context, this is not inconsistent with applicants' adoption of the

USP definition, nor does it support the assertion that it supports an "alternative definition" to the exclusion of the USP definition.

One of ordinary skill in the art would have understood that applicants were not reciting an alternative definition for all "neutral microgranules," but rather were reaffirming only that "particularly valued" embodiments are those that comport with the accepted definition, i.e., having an upper limit of 91.5% sucrose.

One of ordinary skill in the art reading the specification as a whole would have appreciated that applicants' use of the term "neutral microgranules" is consistent throughout the specification. Applicants state that "in the prior art, neutral microgranules are used for attaching a coating of active principle and are generally coated with a polymer film intended to modify the release of the active principle." Specification, page 7, lines 13-16. Immediately following, applicants repeat the USP definition of neutral microgranules. Specification, page 7, lines 18-22. Nowhere throughout the specification do applicants state or even suggest that their frequent and consistent use of the term "neutral microgranules" is other than as defined by the USP, and as adopted by applicants at page 7 of the specification.

Applicants' reaffirmation of the upper limit of sucrose, as established by the USP, is in no way contradictory to, or an alternative definition of, the USP's description and definition of neutral microgranules.

Applicants further note that "in the prior art, numerous tableting studies have been carried out on uncoated inert granules but no study has been carried out on neutral microgranules." Specification at page 7, lines 36-38. From this, one of ordinary skill in the art would have clearly understood that the neutral microgranules were those as defined by USP.

Applicants then distinguished neutral microgranules from other nuclei, such as those prepared by extrusion/spheronization starting from microcrystalline cellulose, lactose or dicalcium phosphate (Specification, page 8, lines 1-7), or nuclei composed of lactose/microcrystalline cellulose (Specification, page 8, lines 25-28), or granules comprising a dicalcium phosphate/microcrystalline cellulose blend (Specification, page 8, lines 35-39). Neutral microgranules, as defined by the USP, are then distinguished from nuclei comprising microcrystalline cellulose. (Specification, page 9, lines 4-37)

The specification then describes the claimed invention as including a "tablet comprising a low dose of active principle formed from microgranules comprising a directly compressible diluent, characterized in that the directly compressible diluent is composed solely of *neutral microgranules* and in that the active principle is attached as a coating to the neutral microgranules and is not coated with an agent intended to modify its release or to mask its taste." Specification, page 10, lines 22-30 (emphasis added). Applicants thus used the previously defined term "neutral microgranules" to describe the present invention; and contrasted the subject matter of the present invention with the immediately preceding paragraphs that describe tablets comprising low doses of active principle in which the active principle is formulated in modified release granules. Those granules are composed of a neutral nucleus coated with a layer comprising the active principle and then with a polymer layer intended to slow the release of the active principle. Specification, page 10, lines 4-11.

In describing the various art formulations, it would have been quite clear to one of ordinary skill in the art that applicants are consistently employing the USP

definition of "neutral microgranules" to describe the present invention, and to distinguish it over prior art formulations that either do not comprise a neutral microgranule, or comprise a neutral microgranule in combination with other ingredients. Thus, applicants state "in the context of the present invention, the term 'neutral microgranules' is understood to mean essentially spherical granules comprising sucrose and starch." Specification, page 10, lines 33-35. This is entirely consistent with applicants' prior statement: "The United States Pharmacopeia (USP XVII, 1990) describes neutral microgranules as essentially spherical granules comprising between 62.5 and 91.5% of sucrose, the remaining being composed essentially of starch." Specification, page 7, lines 18-22.

The rejection, however, improperly attempts to elevate the significance of the following sentence to the status of an alternative definition. However, that statement merely acknowledges the specified upper limit of 91.5% sucrose, and reaffirms that such limit is especially applicable to *particularly valued* embodiments. It is no substitute for the prior definition of the term "neutral microgranules."

According to the MPEP, when addressing written description support for amended claims, "the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP § 2163.I.B. Here, the requirement is met. Applicants clearly contemplated the use of neutral microgranules having between 62.5 and 91.5% sucrose and the remainder starch, as evidenced by applicants' reference to the USP, and explicit recitation and adoption of that definition. The mere fact that applicants reaffirmed that a particularly preferred embodiment of the invention has an upper limit of 91.5% sucrose does not

deviate from or alter that fundamental definition, nor does it suggest that applicants were not in possession of the invention as now claimed. On the contrary, it reaffirms that applicants were working within that definition.

As the USP definition of "neutral microgranules" is clearly set forth within the specification, and is used uniformly throughout without any clear and unequivocal statement of an intention to use it contrary to its commonly accepted definition, applicants respectfully request reconsideration and withdrawal of the new matter rejection.

Prior Art Rejections

Claims 1 and 3-16 are rejected as unpatentable over USP 4,489,026 (Yalkowsky) in view of USP 4,983,399 (Maish). The rejection fails to make a *prima facie* case of obviousness, and so Applicants traverse the rejection.

The rejection fails to establish that one of ordinary skill in the art working at the time of the invention would have been motivated to combine Yalkowsky and Maish. Even if one had combined Yalkowsky and Maish, there is no cited teaching or suggestion leading one to extract from the respective references the particular teachings required to arrive at the present invention. Further, there is nothing in either Yalkowsky or Maish that would have led one of ordinary skill in the art working at the time of the invention to have a reasonable expectation of success in combining those teachings, or any other teachings of the two references, in an attempt to create a pharmaceutical formulation as claimed. Finally, the two references themselves have inconsistent objectives, and so it would have been entirely unclear as to what result would have constituted success. Indeed, the

objectives are so thoroughly opposed, that the references in fact teach away from each other.

The claims are directed to embodiments of a tablet comprising less than 40 milligrams per gram active principle formed by direct compression of microgranules containing the active principle wherein said active principle is attached as a coating to neutral microgranules and is not coated with an agent intended to modify its release or to mask its taste, and wherein said neutral microgranules are essentially spherical granules comprising between 62.5 and 91.5% of sucrose, the remaining being composed essentially of starch, with a uniform size of between 100 and 200 µm.

Yalkowsky purportedly relates to a process for preparing solid unit dosage forms, such as tablets, of pharmaceutical compositions containing extremely low dosages of active material. Yalkowsky describes uniformly spraying small droplets of substantially uniform size of a dilute solution of a pharmaceutically active material onto finely divided, inert, pharmaceutically acceptable excipient particles, and evaporating the solvent to deposit a large number of very small solid particles of the active material onto the excipient particles. The objective is to provide a very low, but highly uniform, concentration of the active material on the particles, and then form the particles into solid unit dosage forms.

Yalkowsky describes particles with active material "having a maximum mean particle diameter in the range of from about 0.5 to about 10 µm." Further, "the coefficient of variation of the particle diameters . . . is variable up to about 100%." Yalkowsky, column 6, lines 49-53 (emphasis added). Further, "by providing a solid unit dosage form in which the pharmaceutically active material is present in the form

of a very large number of very small particles having the selected maximum mean particle diameter...." Yalkowsky, column 6, lines 53-59 (emphasis added).

Producing a very large number of very small particles is critical to the achievement of Yalkowsky's objective, i.e., a solid unit dosage form containing a small amount of active material with highly uniform distribution. Yalkowsky, column 2, lines 52-58. The "very small particles" range from about 0.5 to about 10 μm with a deviation of about 100%. Accordingly, the very small particles are no larger than 20 μm (100% larger than the upper limit of 10 μm).

Yalkowsky teaches that formulations having mean particle size greater than 10 μm cannot pass the Content Uniformity Test. Yalkowsky, column 2, lines 32-37; see also, column 2, lines 42-47 ("In order to ensure uniform distribution of potent drugs in solid unit dosage forms that contain very low dosages of the drug, so that said unit dosage forms will pass the Content Uniformity Test, it is necessary to provide the drug in the physical form of extremely fine particles." emphasis added). In order to abide by the principles and objectives of Yalkowsky's process, one must use extremely fine particles, i.e., mean diameter less than 10 μm, and in no event greater than 20 μm.

The claimed tablets, however, are substantially greater in size and well outside that range. Thus, Yalkowsky teaches away from the present invention.

Further, Yalkowsky does not teach or suggest the use of the USP neutral microgranules as specified in the instant specification and claims. Yalkowsky's "inert powder" used as the "excipient powder" comprise various ingredients, none of which are said to be sucrose. Yalkowsky, column 4, lines 40-45 ("for example, lactose, starch, calcium carbonate, titanium dioxide, silicon dioxide, dicalcium phosphate,

microcrystalline cellulose, sodium alginate, calcium sulfate, talc, or any similar GRAS-listed powder are suitable for use as the excipient powder in the present invention.") Thus, Yalkowsky do not teach or suggest applying the active material on neutral microgranules as expressly required by the instant claims.

One of ordinary skill in the art would not have been motivated to combine Yalkowsky with Maish. Even if there were such a motivation, there is no demonstrated teaching or suggestion leading one to select the specific teachings of those references required to arrive at the claimed invention.

Yalkowsky is directed to the formulation of very small particles having very low concentrations of active ingredient. The many small particles of Yalkowsky range in diameter from about 0.5 to 10 μm, but may deviate to achieve a diameter of 20 μm. In contrast, Maish describes a direct compression carrier composition having a cellulose carboxylic acid ester powder having particle size distribution of 70 to 200 μm. This is well outside the range of particle sizes to which the Yalkowsky process is restricted. The particle size distribution of Maish's cellulose ester powder is necessary to achieve the cumulative weight percent of cellulose ester powder in the formulation. See, e.g., Maish, column 2, lines 3-25. Thus, Yalkowsky and Maish use different matrices, and, not surprisingly, teach the necessity of particles in decidedly distinct size ranges.

Maish also has a fundamentally different objective than that of Yalkowsky. Maish's express objective is to formulate a direct compression carrier composition that maximizes, rather than minimizes, quantity of active agent. Maish describes achieving active agent concentration "greater than about 40 weight % of the formulation." Maish, column 2, lines 44-49; see also Maish, column 1, lines 60-65

(contrasting the prior art by noting that "the maximum amount of physiologically active compound which can be blended with microcrystalline cellulose is approximately 40 weight % based on the weight of the blend.").

One of the ordinary skill in the art would interpret Maish to teach that cellulose ester particulate material is an essential component of those formulations. Maish teaches that the cellulose ester particulate material is "at least 30 weight %" of the direct compression carrier composition. Maish, column 2, lines 54-57. From Maish's discussion, the cellulose ester carrier fulfills various objectives including a support matrix for the active agent, compressibility, and a free flowing particulate. One of ordinary skill in the art, reading Maish would conclude that the cellulose ester particulate material is the carrier and would be used in place of Yalkowsky's excipient powder.

Maish likewise fails to teach or suggest the neutral microgranules described by applicants as a carrier material. Maish states that the cellulose ester particulate material can be used in combination with other known carrier materials such as microcrystalline cellulose, starch, calcium phosphate, dextrose, lactose and the like. Maish, column 2, lines 50-54. One of ordinary skill in the art, however, would understand that such additional carrier materials are merely adjuncts to the principle ingredient of the carrier composition, i.e., cellulose carboxylic acid ester powder. Further, Maish does not suggest the use of neutral microgranules of sucrose and starch, much less using such granules in place of cellulose ester particulate material. Thus, both the carriers and particle sizes of the two references are distinct, and neither reference, either alone or together, teaches or suggests the neutral microgranules of the present invention having the specified size range.

Assuming, only for the sake of argument, that one of ordinary skill in the art might have been motivated to borrow some aspect of the Maish reference and apply it to the Yalkowsky reference, the most likely ingredient preserved from Maish would have been cellulose carboxylic acid ester power. This ingredient, however, would undoubtedly replace the excipient powder of Yalkowsky. Further, there is no demonstrated motivation to combine such material with the formulation of Yalkowsky as the two are directed to fundamentally different objectives, i.e., Yalkowsky to produce a tablet of minimal but uniform active agent; whereas Maish strives for maximal concentration of active agent. See e.g., Maish, column 5, lines 20-25 ("my invention is particularly suitable for use in the preparation of tablets containing high concentrations, e.g., greater than 40 weight % based on the weight of the tablet, of one or more medicaments."). Not only is there no demonstrated motivation for combining these two references, the opposing purposes of the references make it abundantly clear that one of skill in the art would interpret the two references as mutually incompatible.

Assuming for the sake of argument alone that one were motivated to combine Maish and Yalkowsky, there is no support for the assertion that the resulting composition would resemble the claimed invention. On the contrary, within the context of the two disclosures, and taking the two disclosures as a whole, one of ordinary skill in the art would undoubtedly have come up with a fundamentally different composition. Given the divergent objectives, and the use of distinct materials having differing physical and chemical properties, there is no identified reasoning or logic likely to lead one to the instant claims. Accordingly, even if one

were to combine the two references, there is no showing that the resultant combination would in any way resemble the claimed invention.

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to call Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

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